

Grand Challenges in Global Health



Grand Challenges in Global Health

Biomarkers

Biomarkers of Gastrointestinal (Gut) Function and Health Funding Opportunity Announcement

To identify and validate biomarkers of gut function to improve the health and development of children in the developing world

Bill & Melinda Gates Foundation

Global Health Discovery
and
Enteric and Diarrheal Diseases

Table of Contents

1	Introduction	3
2	Program Goal	3
3	Background	3
4	Approach.....	5
5	Program Objective and Scope.....	6
6	Rules and Guidelines.....	8
6.1	Application Instructions and Review Process	8
6.2	Evaluation Criteria.....	9
6.3	Eligibility Criteria	10
6.4	Allowable Costs	10
6.5	Privacy Notice	10
6.6	Warranty	11
6.7	Intellectual Property	11
7	Research Assurances.....	12
7.1	Data Access Principles.....	12
7.2	Research Involving Human Subjects	12
7.3	Research Involving Animals	13
7.4	Clinical Trials	13
7.5	Indemnification	13
7.6	Coverage for all Sites.....	13
7.7	Regulated Activities	13
7.8	Institutional Review Board (IRB) Approval.....	14
7.9	Provision of Care for Human Subjects Research.....	14
7.10	Use of Animals in Research.....	14

1 INTRODUCTION

We are continuing the mission set forth in the Grand Challenges in Global Health initiative to overcome persistent bottlenecks in creating new tools that can radically improve health in the developing world. Under the foundation's [Enteric and Diarrheal Diseases strategy](#) we announce a new grant program: Biomarkers of Gastrointestinal (Gut or GI) Function and Health. This program aims to identify and validate biomarkers or biomarker signatures (a unique pattern of biomarkers indicating a normal or abnormal condition or biological process) that accurately reflect the physical and physiological integrity of the gut in children in the developing world. Ultimately, biomarkers of interest will be sensitive, quantitative indicators that can be correlated with outcomes such as nutrient absorption, failure of linear growth (stunting), and cognitive development—all of which can be impacted by enteric infections and malnutrition.

Note: Two related funding opportunities within the Grand Challenges in Global Health initiative are also being announced this fall: *Discover New Ways to Achieve Healthy Growth*¹ and *Preventing Preterm Birth*.² The *Discover New Ways to Achieve Healthy Growth* program seeks to prevent outcomes caused by the adverse effects that nutritional deficiencies, infections, and environmental toxins can have on healthy developmental processes including: growth restriction, stunting, wasting and impaired cognitive development during the first 1,000 days following conception (-9 to 24 months) in the developing world. The *Preventing Preterm Birth* program aims to explore the underlying mechanisms leading to preterm birth or stillbirth (associated with preterm birth) with emphasis on the role of infection, inflammation, and poor nutrition. Researchers with new ideas and approaches addressing either of these topics are encouraged to respond with submissions to the appropriate program; proposed activities that align with the goals of these related programs will be considered outside of the scope of the Biomarkers of Gastrointestinal Function and Health program.

2 PROGRAM GOAL

The goal of this opportunity is to identify and validate biomarkers of gut function to improve the health and development of children in the developing world. This funding initiative is intended to identify a promising biomarker or a biomarker signature that accurately reflects physical and physiological properties of the structural and/or functional integrity of the gut—especially the ileum or small bowel.³

3 BACKGROUND

The gastrointestinal tract is the exclusive interface with everything that is consumed from the environment by the host and is responsible for the uptake of all micro- and macronutrients, extraction and exclusion of toxins and waste, and metabolism and biosynthesis of critical molecules. It is also the

¹ For more details, see the *Discover New Ways to Achieve Healthy Growth* funding opportunity at www.grandchallenges.org

² For more details, see the *Preventing Preterm Birth* funding opportunity at www.grandchallenges.org

³ This initiative is designed to be complementary to, but not overlapping with, other projects funded by the Bill & Melinda Gates Foundation in immune biomarkers and microbiome characterization.

largest residence of immune cells in the body, and acts as a physical and immune barrier to pathogens. In addition, the human gut is the natural habitat for a large and dynamic community of microorganisms that participates and regulates gut and systemic functions.

Disturbances in gut function can result in devastating health effects, which are especially notable in young children exposed to new pathogens, antigens and xenobiotics, and inadequate nutrients, since they have the greatest requirements for somatic and brain development. Infants and children born in impoverished settings in which fecal environmental contamination and inadequate nutrition are daily common threats suffer disproportionate risks of: 1) infectious acute diarrheas, 2) ongoing diminished capacity to properly respond to new infections and vaccines, and 3) long term defects in linear growth (stunting), physical development and endurance, and cognitive intellectual shortfalls. These striking changes are seen early in life (less than 2-5 years of age), are not reversible and persist throughout life, representing a life-long shortfall in potential and loss of human capital for these children, their families, and society. Stunting, which is a reliable predictor of developmental shortfalls, is documented in 178 million children globally.⁴ While nutritional security is important for children and their families, the lack of secure nutrition only accounts for one third of the global undernutrition burden; the remaining two thirds is believed to involve recurrent infections and ongoing injury with malfunction of the guts in affected children.⁵ Some efforts have been undertaken to understand the suspected pathobiology of the underlying disorders that lead to the large burden of undernutrition but have been limited in funding and in available tools and technology. The constellation of gut abnormalities that have been noted are variously termed tropical (environmental) enteropathy, tropical sprue, and several less common terms; all conditions are associated with settings of poverty, recurrent gut infections with or without diarrhea, and association with small bowel biopsy (when available) showing loss of surface area and villus height with submucosal inflammatory infiltrate. The clinical and histological abnormalities have been associated with laboratory findings of increased small bowel permeability (e.g. urine lactose:mannitol [L:M] ratio and abnormal test results indicating malabsorption). Despite previous and ongoing efforts, it has been difficult to clearly establish the existence of causative relationships between enteric infections, clinical diarrhea, gut injury, and changes measured in the laboratory with stunting and/or cognitive deficiencies. The inability to uncover such a link is likely due to the presence of many confounding factors related to nutrition and systemic infections (i.e. malaria, HIV, etc.) with the added difficulties associated with performing studies in austere settings and the limitations of currently available tools.

Currently, there are very few identified biomarkers that can be used to measure the status of gut health or injury, and the existing markers are limited in the range of conditions that they detect. Attempts have been made to develop markers in feces indicating an unhealthy gut. For example, fecal calprotectin (FC), lactoferrin (LC) and fecal serine protease (FSP) have been shown to be reliable markers of irritable bowel syndrome (IBS), the latter acting as a diarrhea predominant IBS marker. Plasma nitrate levels are currently used as markers for pediatric gastroenteritis. Citrulline has been shown to act as an indicator for mucosal metabolic capacity. Differential absorption and excretion of inert sugars of various

⁴ Black RE, Allen LH, Bhutta ZA, and Caulfield LE. *Lancet* 2008; 371: 243-60.

⁵ Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, Haider BA, Kirkwood B, Morris SS, Sachdev HP, Shekar M. *Lancet* 2008; **371**: 417-40.

molecular weights (such as L:M ratio mentioned above) and presence of circulating antibodies of gut-derived bacterial antigens (anti-core endotoxin antibody) have been used as markers of permeability. There is a need for biomarkers or biomarker signatures that arise from noninvasive biosamples (blood included) to help in the evaluation of gut function, providing a baseline comparison between a functionally healthy gastrointestinal tract and a pathological condition to guide interventions and preventions.

4 APPROACH

Within the Biomarkers of Gastrointestinal Function and Health research program, candidate biomarkers of interest can span a range of host markers or factors, including cellular proteins, metabolites, markers of tissue injury/repair or acute inflammation, or systemic markers (such as hormones) that would be indicative of gut function (or dysfunction) and status. Applicants must provide a description of the methods for testing and analysis of candidate biomarkers, including plans for determining quantitative levels of the biomarkers or biomarker signatures, if applicable. Proposals should be centered on the development of methods for the evaluation of candidate biomarkers or biomarker signatures that also focus on analyses that can be performed directly on patient samples or with minimal processing or stimulation steps. Acceptable sample types and model systems for biomarker discovery and validation include well-characterized patient samples and animal models. For patient samples, proposals must minimally include activities to investigate well-characterized stool samples and may also extend studies to include urine, blood, and saliva samples if linked to the digestive system. For animal models, proposals must minimally propose activities to characterize gut function in healthy animals followed by challenges with toxins, pathogens, or incomplete dietary supplementation to induce changes in gut function or health. Collection and comparative analyses of 'before' and 'after' samples for biomarker discovery and validation studies should follow. The ultimate interest in the use of animal models stems from the added capability of sampling the small bowel or the collection of other biospecimens which cannot be routinely sampled and assessed in clinical studies. Animal systems recapitulating enteropathy or more chronic gut-related conditions are also acceptable, however any proposed animal study must yield results that are translatable to humans and can be correlated with outcomes in children such as nutrient absorption, failure of linear growth (stunting), and cognitive development – all of which can be impacted by enteric infections and malnutrition.

Potential proposers with no direct access to clinical samples or animal models are strongly encouraged to identify a collaborator with such resources and/or capabilities prior to responding to this request for proposals (RFP). The exploration of existing clinical samples is greatly preferred. However, the Bill & Melinda Gates Foundation recognizes that certain biomarkers or biomarker signatures may exist or be measurable only in specific sample types and may consequently require new sample collecting activities.

The Bill & Melinda Gates Foundation is willing to fund up to a total of \$9M for the discovery and validation of biomarkers or signatures of biomarkers that accurately reflect the physical and physiological integrity of the gut that would be applicable to assessing the health of children in the developing world. Proposals for funding are eligible for up to \$1.5M total cost per project. Individual

program budgets should be representative of the scope and magnitude of the proposed studies. The proposal should clearly identify decisions and endpoints that will fit within the proposed budget and time frame of not more than 24 months. Allocation of funding will depend on a number of factors, including relevance of the proposed work to reach validated biomarkers for evaluating the functional status and health of the gut; scientific innovation and merit; clarity of the work plan, including defined go/no go decision points; and criteria to select among biomarker candidates.

Proposals submitted for consideration must clearly state the key challenges and roadblocks relevant to the specific question being addressed and the key hypotheses to be tested by the proposed work plan. They must also demonstrate the direct relevance of the project goal and pathway in contributing to the acceleration of methods development for gauging gut health, outline the critical pathways required to achieve the goal, delineate a well-developed work plan that will proceed along the proposed pathways using clearly defined criteria to down-select among the candidate biomarkers proposed, and define a clear end-project point and metrics of success.

5 PROGRAM OBJECTIVE AND SCOPE

The purpose of this RFP is to solicit new ideas and potential collaborations from academic, industrial and other expert investigators for the discovery and validation of biomarkers or biomarker signatures that would be indicative of a healthy functional or injured GI tract in order to facilitate the future development of robust diagnostic tests for use in pediatric populations in low resource settings. It should be recognized that there may be differences in the pathophysiology of gut dysfunction in infants under the age of 2 years and in children over 2 years of age, which could subsequently impact the types of or levels of biomarkers and/or biomarker signatures. Proposers are encouraged to focus on infants under 2 years of age, when possible, and should not pursue studies on children over 5 years of age as this is a critical window of time when many crucial developmental processes are occurring and pathophysiological processes at this stage can have serious negative and irreversible consequences for health in infancy, childhood, and adulthood. Successful applications must include a strong rationale based on preliminary published or unpublished data for the selection of candidate biomarkers, or biomarker signatures, and methods. Successful applications must also be based on a sound statistical analysis of the number of samples required for validation, a clear analysis plan, and criteria by which the data generated will be evaluated to determine the utility of taking one biomarker or a set of biomarkers forward for future test development.

The term “biomarker” is intended to broadly include host markers or factors that could include cellular proteins, metabolites, markers of tissue injury/repair or acute inflammation, or systemic markers (such as hormones) that would be indicative of healthy gut function (or dysfunction) and status. The biomarkers to be discovered as a part of the proposed work should be relevant to the assessment of samples collected from individuals that may be at risk of disorders or infections capable of causing the previously mentioned types of gut injuries among children in the developing world. Additionally, putative biomarkers should be present in an assayable, stable form in a clinical sample type that can be

easily and rapidly collected; noninvasive sample collection procedures will ultimately be highly preferred.

Topics that would be considered **within** the scope of this program are listed below. These topics are not presented in a specific order nor is the manner in which they have been categorized intended to be exclusive. In responding to the RFP, applicants are encouraged to identify the topic or topics which their proposal aims to address.

Topic Areas of Interest:

Topic 1: Investigation and validation of factors involved in retaining healthy gut lineages or normal barrier functions and intestinal permeability; markers could include the extracellular domain of receptors of epithelial cells or other measurable characteristics.

Topic 2: Studies on and discovery of markers associated with epithelial injury and repair or acute inflammation, such as matrix metalloproteinases, kinases, caspases, cytokines, eicosanoids, hormones, or other molecules that could be definitively traced back to gut pathogenesis or dysfunction.

Topic 3: Examination and discovery of markers indicating the functional status of the gut's ability to absorb, transport, and secrete major nutrients, including carbohydrates, proteins, and fatty acids.

Topic 4: Analysis and identification of hormonal markers involved in autonomic, neuroendocrine functions of the digestive system relevant to gut function or dysfunction making them applicable to the goals of the RFP.

Topic 5: Elucidation of systemic markers that influence or are associated with linear growth or cognitive development in children where the markers have purported or well-defined linkages to malnutrition or gut health.

Proposed activities aligned with the goals of the two related RFPs mentioned in the introductory section fall **outside** the scope of this program. This would include research efforts that are focused on: 1) preventing outcomes caused by the adverse effects that nutritional deficiencies, infections, and environmental toxins can have on healthy developmental processes including: growth restriction, stunting, wasting and impaired cognitive development during the first 1,000 days following conception;⁶ and 2) the exploration of the underlying mechanisms leading to preterm birth or stillbirth (associated with preterm birth) with emphasis on the role of infection, inflammation, and poor nutrition.⁷ Proposers

⁶ For more details, see the *Discover New Ways to Achieve Healthy Growth* funding opportunity at www.grandchallenges.org

⁷ For more details, see the *Preventing Preterm Birth* funding opportunity at www.grandchallenges.org

should use their best judgment and understanding of the three related programs to respond to the opportunity that most directly relates to their idea and approach.

Some additional examples of topics that would be considered **outside** the scope of this program:

- Technology development for new measurement platforms.
- Research on the elucidation of markers associated with mounting a specific adaptive or innate immune response to a pathogen insult or infection; this topic is being explored by other initiatives within the foundation.
- Identification of microbial markers associated with the gut microbiome that may influence the ability of certain species to colonize the GI tract or the identification of host factors involved in shaping the composition of the gut microbiome into a population that could be defined as healthy or predisposed to future injury; this topic is also being explored by other initiatives within the foundation.
- Identification of genetic factors that predispose individuals to abnormal gut function.
- Studies focused primarily on gastritis, irritable bowel syndrome (IBS) or ulcerative colitis, gluten-sensitive enteropathy or celiac disease, Crohn's disease, or other autoimmune diseases of the GI tract.
- Epidemiological or monitoring studies of a cohort without a specific explanation for the uniqueness of the cohort of choice and a well-developed hypothesis to benefit gut function biomarker discovery.

Projects funded through this Program with promising candidate biomarkers or biomarker signatures at the end of the grant period (up to 24 months) that have demonstrated proof of concept for utility in assessing gut health may be eligible for future support should funds become available.

6 RULES AND GUIDELINES

6.1 Application Instructions and Review Process

A Letter of Inquiry (LOI) in response to this RFP should be submitted no later than January 11, 2012 10:00 AM PST. Submitted LOIs must clearly reference the topic(s) it proposes to address on the title page. The Bill & Melinda Gates Foundation (which may subsequently be referred to as 'the Gates Foundation' or 'the foundation') will evaluate the LOIs and applicants who have projects of further interest to the Gates Foundation will be invited in March 2012 to submit a full proposal in April 2012. These time periods are subject to change. All applicants will be notified by email in a timely manner of any change to the dates for notification and proposal deadline. Instructions on the preparation of full proposals will be provided to selected applicants. Due to expected high volumes, the Gates Foundation will not be able to provide individual feedback for LOIs not selected to submit full proposals. The foundation may use external reviewers to assess the merit of proposals; final selection decisions will be made by the foundation. The foundation is willing to fund up to a total of \$9M for the discovery and validation of biomarker(s) or biomarkers signatures of gut function to improve the health and development of children in the developing world. Proposals are eligible for up to \$1.5M total cost per

project for a time frame that is not to exceed 24 months. An invitation to submit a proposal does not guarantee that the foundation will award a grant to the applicant. The foundation may amend or cancel this RFP at any time

LOIs must be submitted electronically, using the forms and process described at the following address

http://www.grandchallenges.org/biomarkers/Pages/Gut_Function_Biomarkers.aspx

Table 1 Application Schedule

Key Dates and Deadlines	Events
November 7, 2011	System open to accept Letters of Inquiry (LOI)
January 11, 2012 10:00 AM PST	Application deadline for LOIs
March 2012	Invitation for submission of full proposals
April 2012	Application deadline for full proposal

6.2 Evaluation Criteria

Significance. Is the approach likely to deliver validated biomarkers that accurately reflect the physical and physiological integrity of the gut in children in the developing world? Could the biomarkers proposed facilitate the future development of robust diagnostic tests for use in pediatric populations in low resource settings? Do the biomarkers proposed represent an important advance in the field through an innovative approach, robust validation plan, and/or potential to test a long standing but as yet unproven candidate marker?

Approach. Are the conceptual framework, design, methods, and analyses innovative, adequately developed, well integrated, and appropriate to the aims of the proposal? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is the likelihood of successful project completion high? Are the proposed time line and milestones appropriate, feasible, and technically sound?

Best Value. Proposals will be evaluated for the cost of the proposed effort relative to the complexity of the proposed work and the degree of risk and advancement proposed. Proposals that have execution plans which represent particularly thoughtful and efficient use of resources will be preferred over proposals representing comparable efforts that do not represent the same value for the investment.

Organizational and Investigator Capability. Is the research team appropriately trained, experienced, and positioned to carry out this work? Is there strong evidence of substantive organizational capability and commitment? Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments

including partnerships with industry or employ useful collaborative arrangements? While the foundation fosters collaborations and formation of consortiums, these will have to be set up by the proposer, as this will not be done by the foundation.

6.3 Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies or other recognized institutions that can successfully execute the activities in their technical area.

6.4 Allowable Costs

Grant funds may be used for the following costs. Please provide budget estimates according to these categories: personnel; required travel; supplies; contracted services; sub-grants and consultants. Partial or full support for equipment may be requested subject to the following circumstances. Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether the Bill & Melinda Gates Foundation will permit purchase of equipment with a depreciable life that is greater than the grant period being requested. In such cases, leasing would be preferable.

Indirect costs: The Bill & Melinda Gates Foundation provides limited indirect cost in accordance with its policy. Prior to submitting an LOI, please review the foundation's indirect cost policy at http://www.gatesfoundation.org/grantseeker/Documents/Indirect_Cost_Policy.pdf

Travel funds are required to participate in one RFP-related meeting per year for up to 4 key members of the project team. Meetings will possibly be held at an international venue.

6.5 Privacy Notice

To help The Bill & Melinda Gates Foundation staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to the Bill & Melinda Gates Foundation (collectively, "Submission Materials") will become the property of the Bill & Melinda Gates Foundation and may be subject to external review by independent subject matter experts and potential co-funders in addition to analysis by the Bill & Melinda Gates Foundation staff. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, the Bill & Melinda Gates Foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission, and whether more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, the Bill & Melinda Gates Foundation may publicly disclose all information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

6.6 Warranty

By providing any Submission Materials, the sender warrants the Bill & Melinda Gates Foundation that they have the right to provide the information submitted. Applicants with questions concerning the contents of their Submission Materials may contact the Bill & Melinda Gates Foundation at: grandchallenges@gatesfoundation.org

6.7 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products that will result in improved diagnostics for those that need of them most in the developing world, the successful development of these high priority products may require substantial involvement and support of private sector industries as sub-contractors, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. It is the intent of this program to support the formation of appropriate public-private partnerships that are essential to meet these urgent global health needs. Intellectual property (IP) rights and the management of IP rights are likely to play an important role in achieving the goals of this program. To this end, the foundation requires that, even at the LOI stage, all applicants seriously consider their willingness to submit a full proposal in compliance with the foundation's proposal guidelines, a portion of which asks for certain information and intentions regarding intellectual property and global access concerns. Specifically, the Bill & Melinda Gates Foundation requires that you agree to use good faith efforts to conduct and manage the research, technologies, information and innovations involved in the Project in a manner that enables (a) the knowledge gained during the Project to be promptly and broadly disseminated, and (b) the intended product(s) to be made available and accessible at reasonable cost to the developing countries of the world. The foundation refers to this as "Global Access."

As part of the foundation's review and evaluation of each full proposal, due diligence will be conducted with respect to each participant's ability and commitment to manage intellectual property in a manner consistent with the stated scientific and charitable goals of the Bill & Melinda Gates Foundation. Due diligence activities may include inquiry into an applicant's:

- 1) Freedom to operate (FTO) and ability to freely use and acquire needed background technology;
- 2) Commitment to promote the utilization, commercialization and availability of inventions for public benefit in developing countries

In order to facilitate this due diligence process applicants are encouraged to provide information with respect to the items above in their submission materials. Applicants should consider whether the protection through IP (in particular through patents) of biomarker(s) or signatures of biomarkers or their validation would best further the goals of this project to improve the health and development of children in the developing world. To be clear, the goal is not to develop a position for or against such IP, but to articulate the role that IP would play in furthering the specific goals of this project.

Applicants will be required to prepare a Global Access Strategy reflecting how they will achieve the Global Access requirements described above.

Applicants are also expected to make new information and materials known to the research and medical communities in a timely manner through publications, web announcements, progress reports to the foundation, and other appropriate mechanisms. These concepts may be discussed at some length with the applicants invited to submit full proposals, and will be addressed (to the extent appropriate) within each final grant agreement. The Global Access Strategy will also include provisions defining these concepts.

7 RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, the Bill & Melinda Gates Foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

7.1 Data Access Principles

In accordance with its charitable mission, the foundation is committed to optimizing the use of health-related data to translate knowledge into life-saving interventions. To this end, it is essential that data are made widely and rapidly available to the broader global health community through good data access practices.

Data access is intended to promote:

- *Innovation*, by encouraging diversity of analysis and opinion, facilitating evaluation of alternative hypotheses, permitting meta-analysis, and facilitating synthesis of results from individual projects into a larger whole, thereby promoting potentially lifesaving new insights.
- *Collaboration*, between teams and institutions, and among diverse disciplines, resulting in greater productivity and creativity.
- *Efficiency*, by preventing unnecessary duplication of effort, enabling secondary analyses of existing data, and enabling the redirection of resources to the most promising research endeavors, thereby maximizing the potential impact of investments.
- *Accountability*, by encouraging independent verification and analysis, thereby improving data quality
- *Capacity Strengthening*, by facilitating the education of new researchers and evaluators and enabling broader access to data for secondary analysis, which is of particular importance to investigators in developing countries.

7.2 Research Involving Human Subjects

You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site (see below sections for more information).

7.3 Research Involving Animals

You agree that no funds will be expended on studies involving animals until all requisite approvals are in place for each site (see below sections for more information). For purposes of this provision, an “animal” is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes.

7.4 Clinical Trials

We expect that projects in the Biomarkers of Gastrointestinal (Gut or GI) Function and Health Program may require clinical trials on human subjects; a condition of this grant is your agreement that the appropriate Institutional Review Boards (“IRBs”) and ethical committees will review and approve the clinical protocols prior to trial initiation. You further agree to conduct clinical trials associated with the project under the generally accepted principles of “Good Clinical Practices” as defined by the International Conference on Harmonization (ICH) E-6 Standard, the United States Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA), as applicable. You acknowledge and agree that, as between you and the foundation, you take and will have full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies, both for yourself and all other sites included in the project, including those activities conducted through sub-grants, subcontracts or other collaborative efforts. You acknowledge and agree that any activities by the foundation as the grantor funding the Project, including its review of the Proposal or suggested modifications to the Project, does not modify the provisions of this paragraph or constitute the basis for any claim by you against the foundation.

7.5 Indemnification

For all clinical trials, the foundation requires that you agree to indemnify, defend and hold the foundation harmless from and against any and all liability, loss, and expense (including reasonable attorneys’ fees and expenses) or claims for injury or damages arising out of or resulting from, or that are alleged to arise out of or result from, the actions or omissions by you or of any of your officers, agents, employees, subgrantees, contractors or subcontractors with respect to the grant. You agree that any activities by the foundation in connection with the Project, such as its review or proposal of suggested modifications to the Project, will not modify or waive the foundation's rights under this paragraph.

7.6 Coverage for all Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies’ approvals are obtained.

7.7 Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; clinical trials, including management of data confidentiality; research involving animals; research using substances or organisms classified as Select

Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

7.8 Institutional Review Board (IRB) Approval

You agree to obtain the review and approval of all final protocols by the appropriate IRBs and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to the foundation if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

7.9 Provision of Care for Human Subjects Research

In keeping with “Good Clinical Practice” standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should similarly be developed, approved and implemented with notice to the employees.

7.10 Use of Animals in Research

You agree to be responsible for the humane care and treatment of animals in projects supported in part or whole by Gates Foundation funds; and to adhere to the official guidelines for animal research applicable in the country and locality where the trial is being conducted. No grant funds may be expended on studies involving animals until all requisite approvals are in place, and notification to that effect has been provided to the foundation. For purposes of this provision, an “animal” is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes. In the case of multi-national collaborations, the standards of each country may be followed, as long as (i) differences do not interfere with the design and analysis of the Project, and (ii) regulations in your institution and host country do not conflict with the management of the Project.

You agree to take responsibility for compliance of all subgrantees or subcontractors (if any) with the appropriate animal welfare laws, rules and regulations. You must report annually as a part of your progress report that the activities are being conducted in accordance with applicable laws in each respective venue (e.g., U.S. grantees must use the U.S. Public Health Service standards. Non-U.S. grantees may cite national laws or the CIOMS International Guiding Principles for Biomedical Research Involving Animals (see http://www.cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm) if there is not a relevant national standard.